Remarks

Claims 1-16, 20-29, and 48-54 are pending in the application. Claims 20-29 are withdrawn from consideration.

Claims 1, 9, and 48 are amended to state, *inter alia*, "wherein the subject does not have symptomatic cardiovascular disease". Claims 2 and 12 are amended to further describe the method. Support for the claim amendments may be found in the specification as filed. *See, for example*, page 18, lines 4 to 17; page 27, lines 17 to 19; page 31, lines 14 to 16.

Claims 48 and 51 are amended herein to recite that a senescent cell is viable but does not divide. Support for the claim amendments can be found throughout the specification such as on page 12, lines 23-25.

New claim 54 is added herein. Support for new claim 54 can be found throughout the specification, such as on page 14, lines 10-24.

No new matter is added. Applicants respectfully request reconsideration of the application in view of the foregoing amendments and following remarks.

Allowable Subject Matter

Claims 51-53 are not subject to any specific rejections or objections. Specifically, claims 51-53 are free of the prior art of record. Allowance of claims 51-53 is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 1, 4-6, 9, 16, and 48-50 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Vasa *et al.*, *Circ. Res.* **89(1)**, E1-E7 (2001). Applicants respectfully traverse.

As amended, claims 1, 4-6, 9, 16, and 48-50 are directed to a method of diagnosing increased vascular function or decreased vascular function or increased cardiovascular risk in a subject, *inter alia*, wherein the subject does not have symptomatic cardiovascular disease.

Vasa et al. discloses that the number of endothelial progenitor cells (EPCs) is reduced in subjects with coronary artery disease as compared to healthy controls. An analysis of the risk factors showed that smokers had reduced levels of EPCs. In addition, EPCs from subjects with CAD had an impaired migratory response. Thus, CAD correlated with a decreased function of EPCs. Vasa et al. suggests that the reduced number and function of EPCs correlates with adult neovascularization.

All the subjects in Vasa *et al.* (*Circ. Res.*) have coronary artery disease (CAD). *See*, Abstract of Vasa *et al.* (*Circ. Res.*) ("The present study demonstrates that patients with CAD revealed reduced levels and functional impairment of EPCs, which correlated with risk factors for CAD" emphasis added). Vasa et al. does not suggest, nor render obvious that a decrease in the number of EPCs will affect vascular function, let alone vascular function in subjects without coronary artery disease. Therefore Vasa *et al.* (*Circ. Res.*) does not anticipate, nor render obvious, claims 1, 4-6, 9, 16, and 48-50 as amended.

Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 9-11 and 16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Vasa *et al.*, *Circulation* **103(24)**, 2885-2890 (2001). Applicants respectfully traverse.

As amended, claims 9-11 and 16 are directed to a method of diagnosing increased vascular function in a subject without symptomatic cardiovascular disease, comprising assaying the number of endothelial progenitor cells in a blood sample from the subject. A decrease in the number of endothelial progenitor cells in the sample as compared to a control indicates decreased vascular function.

Vasa et al. describe that patients with coronary artery disease (CAD) were treated with atorvastatin. Statin treatment of patients with CAD was associated with an increase in the number of circulating endothelial progenitor cells. Statin treatment resulted in the endothelial progenitor cells having an increased migratory capacity in response to vascular endothelial growth factor. Thus, Vasa et al. suggest that the increase in the number of EPCs resulting from statin treatment contributes to angiogenesis and vasculogenesis that leads to neovascularization. Vasa et al. does not suggest that a decrease in the number of EPCs would lead to a decrease in vascular function, such as vascular contractility, brachial reactivity, arterial hyperplasia or mophometric parameters.

All the test subjects in Vasa *et al.* (*Circulation*) have coronary artery disease (CAD). *See*, Abstract of Vasa *et al.* (*Circulation*) ("The results of the present study define a novel mechanism of statin treatment in patients with stable CAD" emphasis added). Vasa et al. does test the effect of statin treatment in healthy subjects, but this is only as a control population. Vasa et al. does not suggest, nor render obvious assessing vascular function in either the subjects with stable

CAD or the controls. Moreover, Vasa et al. does not suggest that changes in the number of EPCs have any effect in the healthy controls.

Therefore Vasa *et al.* (*Circulation*) does not anticipate, or render obvious, claims 9-11 and 16 as amended.

Rejections under 35 U.S.C. § 112

Claims 2-3, 7-8, 12-15 and 48-50 are rejected under 35 U.S.C. § 112, second paragraph, for being indefinite. Applicants respectfully traverse.

Claims 2 and 12 are rejected under 35 U.S.C. § 112, second paragraph as allegedly they "are indefinite because it is unclear how the endothelial progenitor cells ... are assayed by merely subjecting a mixed population of non-adherent blood cells." Claims 2 and 12 are amended herein to clarify the steps in the method, rendering the rejection moot.

Claims 48-50 are rejected under 35 U.S.C. § 112, second paragraph as allegedly the "senescent" endothelial progenitor cells are indefinite, as there are not specific phenotypic features that delineate a senescent cell in view of a non-scenescent cell. Applicants respectfully disagree with this rejection.

The term "endothelial progenitor cell" is defined in the specification as filed on page 7, line 31 to page 8, line 27, and the term "senescence" is defined on page 12, lines 23 to 25.

M.P.E.P. § 2173.02 sets forth that the test for definiteness under 35 U.S.C. § 112, second paragraph, as whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986). In light of the definitions provided in the specification, one of skill in the art would easily understand the term "senescent endothelial progenitor cells" refers to endothelial cells that "is viable but does not divide" (see the specification at page 12, line 23-25). A non-senescent endothelial progenitor cell is viable, divides, and expresses a number of phenotypic markers (see the specification at page 7, line 30 to page 8, line 17). Therefore, Applicants submit that claims 48-50 are definite under 35 U.S.C. § 112, second paragraph. However, solely to advance prosecution, claims 48 and 51 are amended herein to clarify that a

senescent endothelial progenitor cell is an endothelial progenitor cell that has reached the end of its proliferative capacity so that it is viable but cannot divide.

In view of these remarks, and the amendment of the claims, reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants believe that this application is in condition for allowance, which action is requested. If any issues remain, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office Action in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: 503-595-5300
Facsimile: 503-595-5301

By _____
Susan Alpert Siegel, Ph.D.
Registration No. 43,121